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DA-9701: A New Multi-Acting Drug for the Treatment of Functional Dyspepsia

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Abstract

Motilitone® (DA-9701) is a new herbal drug that was launched for the treatment of functional dyspepsia in December 2011 in Korea. The heterogeneous symptom pattern and multiple causes of functional dyspepsia have resulted in multiple drug target strategies for its treatment. DA-9701, a compound consisting of a combination of Corydalis Tuber and Pharbitidis Semen, has being developed for treatment of functional dyspepsia. It has multiple mechanisms of action such as fundus relaxation, visceral analgesia, and prokinetic effects. Furthermore, it was found to significantly enhance meal-induced gastric accommodation and increase gastric compliance in dogs. DA-9701 also showed an analgesic effect in rats with colorectal distension induced visceral hypersensitivity and an antinociceptive effect in beagle dogs with gastric distension-induced nociception. The pharmacological effects of DA-9701 also include conventional effects, such as enhanced gastric emptying and gastrointestinal transit. The safety profile of DA-9701 is also preferable to that of other treatments.

Key Words: DA-9701, Functional dyspepsia, Pharmacology, Gastric accommodation, Visceral hypersensitivity, Prokinetics

INTRODUCTION

DA-9701, a new herbal drug for the treatment of functional dyspepsia (FD), was developed by Dong-A Pharmaceutical in Korea. The drug received New Drug Application (NDA) approval in May 2011 from the KFDA (Korea Food and Drug Administration). It is formulated as a 50% ethanol extract from Corydalis Tuber and Pharbitidis Semen.

FD is a complex of dyspeptic symptoms including upper abdominal pain, heartburn, bloating, and discomfort (Stanghellini *et al*., 2003). These symptoms are thought to originate from the upper abdomen but their structural and organic causes are not known (Halder and Talley, 2007). The pathophysiology of FD is not simple, and is known to have multiple causes including delayed gastric emptying, impaired gastric accommodation, visceral hypersensitivity, small bowel dysmotility, genetic factors, social stress, and inflammation (Brun and Kuo, 2010). Among them, impaired gastric accommodation, visceral hypersensitivity and delayed gastric emptying are known to be the major pathophysiological causes of FD (Brun and Kuo, 2010). Fig. 1 shows pathophysiology of FD and drug target. Delayed gastric emptying is a traditional therapeutic target of gastroprokinetics (Stanghellini *et al*., 2004). Visceral hypersensitivity is a common cause of functional gastrointestinal diseases and there is no established treatment for visceral hypersensitivity (Talley *et al*., 2012). However, off-label antidepressants have been frequently prescribed for visceral pain management (Talley *et al*., 2012). Impaired gastric accommodation was reported to be related to early satiety and a

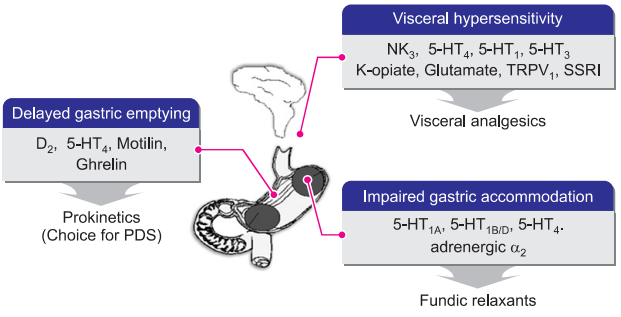

Fig. 1. Major drug targets and main ideal therapies discussed for correction of the pathophysiological causes of functional dyspepsia [modified from (Moro *et al*., 2004)].

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decrease of weight gain. Previously, there have been no treatments termed fundic relaxants (Tack and Janssen, 2011b).

In Rome II criteria (Drossman, 1999), FD was defined as recurrent upper abdominal pain and discomfort for at least 12 weeks during the preceding 1 year. The Rome II classification divided patients having a wide range of dyspepsia symptoms into 4 groups on the basis of the major symptomatic pattern: reflux-like, ulcer-like, dysmotility-like, or nonspecific FD. The criteria excluded patients with predominant heartburn (reflux-like pattern) from the dyspepsia spectrum (Suzuki *et al*., 2006). In Rome III criteria, the definition of FD was less restrictive and had a shorter time frame (3 months of symptoms in the previous 6 months). The symptomatic categorization of Rome II was not reliable because of frequent overlap among irritable bowel syndrome (IBS), gastroesophageal reflux disease (GERD), postprandial distress syndrome (PDS), and epigastric pain syndrome (EPS) (Suzuki *et al*., 2006). Due to this reason, amongst others, the Rome III committee decided to categorize FD into 2 groups for the purpose of therapeutic research and clinical utility: PDS and EPS (Tack *et al*., 2006). Major symptoms of FD include postprandial fullness, early satiety, epigastric pain, and epigastric burning. Nausea, vomiting, and heartburn, which were included under FD symptoms under the Rome II criteria, were moved to other categories.

The prevalence of FD was reported to be about 20% in western countries (Talley *et al*., 1992; Agreus *et al*., 1995; Piessevaux *et al*., 2009). In Korea the prevalence of FD was reported to be 13.4% on using the Rome II criteria, with the dysmotility type being dominant (Rhie *et al*., 2007). On using the Rome III criteria, the prevalence was reported to be 8.1% (EPS, 4.6% and PDS, 6.5%) (Noh *et al*., 2010). FD significantly decreases patients' quality of life and increases social cost.

The multiple mechanisms involved in the pathophysiology of FD seem to make it difficult for a new FD drug to reach a satisfactory efficacy level, or even for it to be appropriately evaluated. Further, opinion leaders worldwide have said that an agent that is able to modulate multiple mechanisms will be more promising than an agent highly selective for a single mechanism and that a new drug for FD should target all or many pathophysiological targets (Camilleri *et al*., 2006). DA-9701 was developed to have multiple action mechanisms by combining herbs, and finally, Pharbitidis Semen and Corydalis Tuber were selected. The pharmacology concerning the multiple action mechanisms of DA-9701 and some associated safety issues are reviewed here.

CURRENT STATUS OF DRUG DEVELOPMENT FOR TREATMENT OF FD

Currently, major drugs prescribed for treatment of FD are gastrointestinal prokinetics. After withdrawal of cisapride due to its cardiovascular side effects, several prokinetic agents were developed to have lower safety concerns. There were numerous attempts to develop new agent for treatment of functional dyspepsia and their clinical study results are summarized in Table 1. Major end point of clinical trial were symptomatic relief and correction of pathophysiological cause such as delayed gastric emptying, impaired gastric accommodation and visceral hypersensitivity. Some of them succeeded in showing efficacy and launched into the market. They are tegaserod, itopride, mosapride, domperidone, metoclopramide, levosulpiride and so on. However, the need for good efficacy and safety is still unmet. Besides, Tegaserod was withdrawn from the market due to cardiovascular side effect and D_2 antagonists were known to induce hyperprolactinemia. The efficacy of these agents is narrowed to prokinetic effect. Recently acotiamide and STW 5 were launched into market. Acotiamide, a muscarinic antagonist was developed as prokinetics but failed to correct delayed gastric emptying in clinical trial while showing symptomatic relief and lack of dose response (Tack and Janssen, 2011a). Besides, the dose of symptomatic relief and efficacy for increasing accommodation didn't match (Tack and Janssen, 2011a). STW 5 (Iberogast®) is a phytomedicine consisted of nine herbs. It as a leading phytomedicine has been used for more than 40 years (Rosch *et al*., 2006) and studied abundantly. Interestingly acotiamide has been known to increase gastric accommodation and STW 5 also has multiple action mechanism including fundus relaxation (Schemann *et al*., 2006). Moreover, DA-9701 has been known to increase gastric accommodation *in vivo* (Kim *et al*., 2012) beyond prokinetic effect and visceral analgesic effect. These new agents and the efficacy on fundus relaxation seem to reflect increasing importance of gastric accommodation in pathophysiology of FD. Multiple action mechanism including fundus relaxation efficacy may be more suitable for chronic complex disease than single action, which will be verified before long.

DA-9701: A HERBAL COMBINATION

DA-9701 is formulated with Pharbitidis Semen and Corydalis Tuber. Corydalis Tuber had been used in traditional medicine for the treatment of gastric (Soji *et al*., 1969) and duodenal ulcers (Kamigauchi and Iwasa, 1994) and dysmenorrhea (Jia *et al*., 2006). Extracts from Corydalis Tuber have been used as antispasmodic agents for the gastrointestinal tract and as analgesics (Ding *et al*., 2007). Pharbitidis Semen is the seed of Pharbitis nil Choisy of the Convolvulaceae family and has been used as a folk medicine for its analgesic effects on the abdomen (Kumar *et al*., 2009).

Compared to non-botanical drugs, extracts of herbal material mixtures require more complicated quality control. Various analyses were performed for quality certification. The tests included identification of herbal material and extracts, loss on drying, inorganic impurities (like heavy metals), microbial limits, and pesticides, and chemical assays. Botanical materials are complex mixtures of numerous chemical constituents. Highperformance liquid chromatography (HPLC) performed for batch-to-batch control revealed corydaline and chlorogenic acid as the major constituents.

THE PHARMACOLOGY OF DA-9701

The *in vivo* pharmacological study results of DA-9701 were summarized in Table 2 and *in vitro* receptor affinities to major receptor related to gastrointestinal function were summarized in Table 3 including comparison with other prokinetics.

Fundus relaxation effect

Impaired gastric accommodation is one of major therapeutic targets in FD. There are 2 kinds of responses in proximal gastric relaxation. One is "receptive relaxation" (Cannon and

Table 1. Overview of studied prokinetics, fundic relaxants and visceral analgesics in functional dyspepsia

Drug class	Drug name	Clinical trial results
Prokinetics		
5-HT_4 receptor agonists	Cisapride	Accelerated gastric emptying of patients with functional dyspepsia (Degryse *et al.*, 1993)
		Enhanced perception of gastric distension and the gastric accommodation to a meal in health (Tack *et al.*, 1998a)
	Tegaserod	Accelerates gastric emptying and gastrointestinal transit in healthy subject (Degen *et al.*, 2001)
		Enhanced gastric accommodation in health and in FD (Tack *et al.*, 2003b)
		No significant effect on gastric motor and sensory function in healthy individuals (Talley *et al.*, 2006)
	Renzapride	Enhances gastric emptying in health and in diabetic gastroparesis (Mackie *et al.*, 1991)
	Mosapride	Enhances gastric emptying in health (Kanaizumi *et al.*, 1991)
		Phase 2 in FD: no benefit over placebo (Hallerback *et al.*, 2002)
Dopamine 2 receptor antagonists	Itopride	Decreases gastric accommodation in health (Choung *et al.*, 2007)
		Acceleration of gastric emptying: benefit shown by a placebo-controlled trial in diabetic patients (Stevens *et al.*, 2008)
		Phase 2 in FD significant benefit (Choung *et al.*, 2007)
		Phase 3 in FD no benefit over placebo (Talley *et al.*, 2008)
	Levosulpiride	Acceleration of gastric emptying: benefit shown by a randomized trial to be similar to cisapride (Mansi *et al.*, 2000)
	Domperidone	Acceleration of gastric emptying: benefit shown by meta-analysis of a small number of trials (Veldhuyzen van Zanten *et al.*, 2001)
	Metoclopramide	Accelerated gastric emptying in dysmotility-like dyspepsia (Banani *et al.*, 2008)
		Accelerated antral emptying in FD (Dumitrascu *et al.*, 1998)
		Metoclopramide significantly improved delayed gastric emptying (Hancock *et al.*, 1974)
Motilin receptor agonists	Mitemcinal	Enhances gastric emptying in gastroparesis (McCallum and Cynshi, 2007b)
		Phase 2 in diabetic gastroparesis: no benefit over placebo; post hoc potential benefit in subgroups (McCallum and Cynshi, 2007a)
Ghrelin receptor agonists	TZP-101	Enhances gastric emptying in diabetic gastroparesis patients (Ejskjaer *et al.*, 2009)
Fundic relaxants		
Nitrates	Nitroglycerine	Enhances gastric accommodation in health and in FD (Gilja *et al.*, 1997)
PDE inhibitors	Sildenafil	Enhances gastric accommodation in health and delays gastric emptying in health (Sarnelli *et al.*, 2004)
SSRI	Paroxetine	Enhances gastric accommodation in health (Tack *et al.*, 2003a)
5-$HT_{1B/D}$ receptor agonists	Sumatriptan	Enhances gastric accommodation in health and have no influence in antral contraction (Sekino *et al.*, 2012)
Alpha 2 adrenergic agonists	Clonidine	Relaxes stomach and reduces gastric sensation without inhibiting gastric accommodation and gastric emptying (Thumshirn *et al.*, 1999)
5-HT_{1A} receptor agonists	Buspirone	Relaxes the proximal stomach in the fasting state health and delays gastric emptying in healthy volunteers (Van Oudenhove *et al.*, 2008)
	R137696	Relaxes the proximal stomach in health (Boeckxstaens *et al.*, 2006)
		Phase 2 in FD: no benefit over placebo (Tack *et al.*, 2009b)
M1/M2 muscarinic receptor blockers	Acotiamide	May enhance accommodation in FD
		Phase 2a in FD: potential benefit (Tack *et al.*, 2009a)
		Phase 3 in FD: over 4 weeks, significantly improved symptom severity and eliminated meal-Related symptoms in patients with FD (Matsueda *et al.*, 2012)
Visceral analgesics		
5-HT_3 antagonist	Alosetron	Reduction of visceral hypersensitivity (Delvaux *et al.*, 1998)
		Benefit shown by a placebo-controlled trial (Dukes *et al.*, 2000)
Opioid k agonist	Fedotozine	Reduction of visceral hypersensitivity in healthy (Coffin *et al.*, 1996)
		Benefit shown by a placebo-controlled trial (Read *et al.*, 1997)
NK-1 antagonist	Aprepitant	No influence on gastrointestinal motility in healthy volunteers (Madsen and Fuglsang, 2008)
NK-3 antagonist	Talnetant	No effect on rectal compliance or distension-induced rectal sensation in healthy participants (Houghton *et al.*, 2007)

Lieb, 1911), and the other is "adaptive relaxation" (Jahnberg *et al*., 1975), a synonym of accommodation. Receptive relaxation occurs when swallowing foods, and adaptive relaxation initiates with entrance of the chyme to the duodenum and lasts for a period of time. In FD patients, impaired gastric accommodation prevalence was reported up to about 40%, and it was reported that impaired accommodation was related to early satiety and weight decrease (Bisschops and Tack, 2007).

Currently there are limited available animal models for evaluating the fundus relaxing effect. In humans, the barostat method is the gold standard to measure gastric tone and accommodation (Mundt *et al*., 2002; Tomita *et al*., 2013). Most of the well-known studies on fundus relaxation are using barostat in the canine (Azpiroz and Malagelada, 1985; De Ponti *et al*., 2003; Lei *et al*., 2005; Yin *et al*., 2007), but rat (Graca *et al*., 2002; Monroe *et al*., 2004; Romer *et al*., 2005; Zhao *et al*., 2005), ferret (Blackshaw *et al*., 1987) and feline (Mayrand *et al*., 1994; Janssen *et al*., 2004) are also known *in vivo* models. There are 2 kinds of end points evaluating fundus relaxation in the canine barostat model: accommodation and compliance (Azpiroz and Malagelada, 1985; De Ponti *et al*., 2003). The physiological gastric accommodation response enables relaxation of the proximal stomach providing space to receive foods without an increase in gastric pressure (Azpiroz and Malagelada, 1986). Especially meal-induced gastric accommodation is thought to be the most important motor index that can be studied in this model, since it is impaired in FD patients and it is a physiological test (Tack, 2009). Gastric compliance, which is tested in the fasting state, measures gastric tone in the resting state, and seems to be related to pain and discomfort perception threshold (De Ponti *et al*., 2003; Kuiken *et al*., 2005). Sumatriptan, known as a migraine treatment, was reported to enhance gastric accommodation in both humans and canines. Additionally, the triptan class of drugs was reported to have enhancing effects on gastric accommodation in canine (Moro *et al*., 2004). However, currently there is no established fundic relaxant and some agents are in development (Tack and Janssen, 2011b).

It was evaluated that DA-9701 can relax the proximal stomach in dog. The fundus relaxing effect was first established

Table 2. Pharmacological profile summary of DA-9701

Experimental pharmacology				
Study type	Effect studied	Experimental	Result	Reference
In vitro	Modulation of pacemaker activity	Whole cell patch clamp	DA-9701 affect GI motility by the modulation of pacemaker activity in the ICC	(Choi *et al*., 2009)
In vivo	D_2 antagonistic activity	Inhibition of apomorphine-induced delayed gastric emptying in rats	Antagonism of D_2 agonist apomorphine inhibited gastric emptying (3 mg/kg po)	(Lee *et al*., 2008)
In vivo	5-HT_{1A} antagonist activity	Restraint stress-induced feeding inhibition in rats	The stimulatory effects of DA-9701 (3 mg/kg po) were blocked by the 5-HT_{1A} antagonist WAY 100635	Not reported.
In vivo	5-HT_{1A} antagonist activity	Restraint stress-induced impaired fundic relaxation in rats	The fundic relaxing effects of DA-9701 (3 mg/kg po) were blocked by the 5-HT_{1A} antagonist WAY 100635	Not reported
In vivo	Fundus-relaxing activity	Canine gastric compliance with barostat	Active at 0.3 mg/kg po	(Lee *et al*., 2008)
In vivo	Fundus-relaxing activity	Meal-induced gastric accommodation with barostat in dogs	Active at 0.3 mg/kg po	(Kim *et al*., 2012)
In vivo	Gastroprokinetic activity	Gastric emptying in rats	Active at 0.3 and 3 mg/kg po	(Lee *et al*., 2008)
In vivo	Improvement of delayed gastric emptying	Rat gastric emptying delayed by cisplatin treatment	Active at 3 mg/kg po	(Lee *et al*., 2008)
In vivo	Imrovement of delayed gastric emptying induced by stress and inhibition of stress related hormones	Rat, stress induced delayed gastric emptying	Active at 3 mg/kg	(Jung *et al*., 2013)
In vivo	Antinociceptive effect against Colorectal distension induced visceral pain in visceral hypersensitivity rat	Neonatal Colorectal distension induced visceral hypersensitivity	Active at 0.3~3	Not reported
In vivo	Antinociceptive effect in gastric distension induced nociception	Gastric distension induced nociception by barostat	Active 0.3~1	Not reported

using the gastric compliance model, and it was shown that the pressure volume curve was shifted left and up in the DA-9701 treated group (Lee *et al*., 2008). Also, in the meal-induced gastric accommodation model, DA-9701 increased the intragastric volume more than in the vehicle-treated group, and this lasted for more than the normal accommodation response in dog barostat studies (approximately 1 h) (Kim *et al*., 2012). DA-9701 may be effective to treat stress-related disorders because one of its active ingredients (AI), tetrahydroberberine (THB), alleviates impaired gastric compliance in the post-stress rat (Lee *et al*., 2011), and it prevented stress induced feeding inhibition (Kim *et al*., 2010). The common mechanism between stress-induced feeding inhibition and impaired gastric relaxation is not known. However, it is known that THB relaxes the proximal stomach via 5-HT_{1A} agonism (Lee *et al*., 2011) and that DA-9701 significantly inhibits feeding inhibition induced by restraint stress via 5-HT_{1A} activation in the rat (Kim *et al*., 2010). DA-9701 also has 5-HT_4 and adrenergic α_2 agonistic properties but it is not fully established that activation of these receptors effect proximal stomach relaxation. However, there are reports that a 5-HT_4 agonist and an adrenergic α_2 agonist have a fundus relaxation effect (Tack *et al*., 1998a; Tack *et al*., 2004).

Visceral analgesic effect

In the past decade, treatment development for functional gastrointestinal diseases (FGIDs) has focused on gastrointestinal motility. Particularly for IBS, several agents were developed to correct bowel movement, but the overall effect was not sufficient. Thus, visceral hypersensitivity was targeted as an alternative approach for FGID treatment development (Bradesi *et al*., 2008). Visceral hypersensitivity is the lowered perception and pain threshold to visceral stimuli that normal subjects do not perceive, and this is related to the visceral pain experienced by FGID patients (Mayer and Gebhart, 1994). Visceral hypersensitivity was identified as a major therapeutic target of many gastrointestinal disorders, including irritable bowel syndrome, functional dyspepsia, gastroesophageal reflux disease, and gastroparesis. Currently, there is no established agent for correcting visceral hypersensitivity, but several agents are being developed. Psychotropic agents and antidepressants are often used to correct visceral hypersensitivity in FD but the true benefit was not yet been fully proven (Tack and Janssen, 2011b).

There is no other method to evaluate analgesia in animals except through the use of surrogate markers, for example abdominal contraction or change of blood pressure (Mayer *et al*., 2008). Various stimulations inducing pain and discomfort can be used: distension of the lumen of the intestine, chemical irritant contact with the intestine, and parasitic infection. Experimentally, visceral hypersensitivity can also be induced by neonatal maternal separation and neonatal experiences of pain (Al-Chaer *et al*., 2000; Lidow, 2002; Lin and Al-Chaer, 2003; Chung *et al*., 2007a; Chung *et al*., 2007b).

In gastric distention induced nociception model, DA-9701 showed an analgesic effect: the perception of intragastric distension and the perception threshold was increased dose dependently and significantly in canine (unpublished). In colorectal distension induced model also, DA-9701 showed analgesic effect (unpublished). Furthermore corydaline and tetrahydropalmatine, the AI of DA-9701, was known to have antinociceptive effects on visceral and somatic nociception in rats (Wang *et al*., 2010; Cao *et al*., 2011). The pain signal that arises from the peripheral region transfers to the spinal cord (dorsal root ganglion) and there the information is processed for transfer to the central nervous system (CNS). It is certain that DA-9701 has an effect at the pain signal transduction level and is related with downregulation of phosphorylated extracellular-signal-regulated kinase (p-ERK) (unpublished).

DA-9701 has a high affinity to multiple receptors related to gastrointestinal function. Among them, it was suggested that 5-HT_{1A} and adrenergic α_2 might be involved in increased perception and pain threshold. The affinity of DA-9701 to 5-HT_{1A} and adrenergic α_2 receptors are 6.87 and 4.81 μg/ml respectively. 5-HT_{1A} agonism was known to relax smooth muscle (Coulie *et al*., 1999; De Ponti *et al*., 2003), a possible mechanism of increased perception (Kuiken *et al*., 2005) and pain threshold related to tension-sensitive mechanoreceptor inactivation (Blackshaw *et al*., 1987). Moreover, an adrenergic α_2 agonist was known to have antinociceptive effect to visceral, somatic and noxious stimuli (Wang and Mo, 1989; Danzebrink and Gebhart, 1990; Harada *et al*., 1995).

Prokinetic effect

The prokinetic effect was the traditional therapeutic target of FGIDs for the treatment of impaired gastrointestinal motility and the fundamental feature of gastrointestinal prokinetics. Prokinetics was traditionally regarded as the first step of PDS (postprandial distress syndrome), with an assumption that delayed gastric emptying was a major pathophysiological mechanism and that most symptoms arise from it (Tack, 2008). However, delayed gastric emptying did not well corre-

Table 3. Receptor affinities of DA-9701 and related visceral functions

Receptor/Affinity[#]	Related GI** function	DA-9701 (function)**	Cisapride*	Mosapride*	Itopride[##]	Domperidone*
5-HT_{1A}	Fundus relaxation[(1)]	6.87 (agonist)	-	-	-	-
Adrenergic α_2	Visceral hypersensitivity[(2)]	4.81 (agonist)	-	-	-	-
D_2	GI motility[(3)]	0.38 (antagonist)	0.11	-	0.434	0.008
5-HT_4	GI motility[(4)]	13.2 (agonist)	0.019	0.057	-	-
	Visceral hypersensitivity[(5)]					

GI: gastrointestinal.
*Data from Thomson Reuters Integrity, **Values from Eurofins Panlabs assays results, [#]Ki value (μg/ml), [##](Kessler *et al*., 1991).
[(1)]Coulie *et al*., 1999; Herman *et al*., 2008, [(2)]Tack *et al*., 2004, [(3)]Nagahata *et al*., 1992, [(4)]Dumuis *et al*., 1989; Taniyama *et al*., 1991, [(5)]Tack *et al*., 1998a.

late with other symptoms suggesting other causes of the symptoms might be present (Tack *et al*., 1998b; Tack *et al*., 2001).

There are numerous animal models to evaluate the effect of enhanced gastric emptying. In rat, the method of administering a meal and measuring the amount of remaining meal after a period of time is widely used to evaluate gastric emptying. The meals used for experimental purposes vary according to the purpose of the experiment, and include semisolid meals, solid meals, and liquid meals. A pathophysiological model of delayed gastric emptying includes delayed gastric emptying by dopamine, cisplatin, and opioids (Ramsbottom and Hunt, 1970; Tanila *et al*., 1993; Hirokawa *et al*., 1998). Intestinal transit is also widely used for evaluating intestinal motility. A pathophysiological model includes delayed gastrointestinal transit by opioids or postoperative ileus (Galligan and Burks, 1983; Tanila *et al*., 1993). Marker materials used for transit studies include charcoal and FITC-conjugated, amongst others (Miller *et al*., 1981; Williams *et al*., 1992).

The ability for DA-9701 to promote gastric emptying and gastrointestinal transit was evaluated in these models, and showed comparable prokinetic effects with other prokinetics (Lee *et al*., 2008). DA-9701 enhances gastric emptying and gastrointestinal transit via dopamine D_2 antagonism and 5-HT_4 agonism (Lim *et al*., 2012). The receptor affinities of DA-9701 to D_2 receptor and 5-HT_4 receptor are 0.381 and 13.2 μg/ml, respectively (Eurofins Panlabs). There can be some argue on coexistence of relaxation effect and contraction effect on stomach but, it can be explained by one report about serotonergic receptors' distribution in stomach in which contractile receptors were dominant in antrum region and relaxing receptors were dominant in fundus region.

SAFETY OF DA-9701

The LD_{50} of DA-9701 was found to be 2,000 mg/kg as a single treatment, and the no observed adverse effect level (NOAEL) was identified as 150 mg/kg in a pivotal repeated treatment study (26 weeks) in rats. NOAEL was 100 mg/kg in both 1-week and 13-week repeated-treatment studies in dogs. DA-9701 had no genotoxicity. The hyperprolactinemia due to D_2 antagonism, which is one of major mechanisms of action of DA-9701, was one of the safety concerns. The prolactin ED_{200} of DA-9701 was about 70-fold lower than itopride (3.78 vs 270.1 mg/kg) in rats (Fig. 2). The CNS distribution of corydaline, one of the marker compounds of DA-9701, was studied because D_2 antagonists such as metoclopramide had a direct effect on the CNS across the blood brain barrier. The pharmacologically effective concentration of corydaline is greater than 15 μM (Adsersen *et al*., 2007; Ma *et al*., 2008). The distribution of corydaline was not as much enough to have a pharmacological effect based on the blood concentration of 12.42~17.64 nM using the human dose. Chlorogenic acid, another marker compound of DA-9701, does not cross the blood brain barrier. 5-HT_4 agonism is involved in DA-9701 pharmacology, and 5-HT_4 agonist such as cisapride and tegaserod were withdrawn from the market due to adverse cardiac effects. Thus, a single-treatment study in beagle dog and rat was performed using telemetry to assess cardiac safety. No abnormal event was observed up to 250 mg/kg in dog and 100 mg/kg in rat. This is 67- and 167-fold higher than the human dose, respectively.

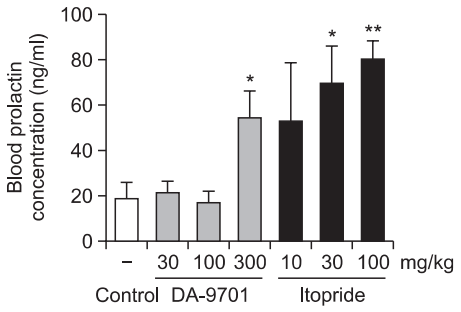

Fig. 2. The comparative blood prolactin elevation effect of DA-9701 versus itopride in SD rat (In briefly, blood was recovered in 30 min after drug administration in 8 weeks old SD rats and the prolactn level was analyzed by Rat PRL Elisa kit (AER011) within 6 hours from recovery. 5 animals were used in each group. Open bar; control, dark gray bar; motilitone, Black bar; Itopride *p<0.05, **p<0.01 vs. control; student's t-test, value of result; Mean ± SD).

SUMMARY

FD is a highly prevalent chronic gastrointestinal disorder that is of considerable burden to both the patient and society. First of all, the pathophysiology should be understood completely for better treatment but, it may be a long way. Multiple action mechanisms may be a good solution for multifactorial and chronic disease. DA-9701 is a leading phytomedicine which implicated the possibility of multiple drug target synergism versus single molecular target against functional dyspepsia which has complex pathophysiology.

DA-9701 showed a beneficial effect on gastric accommodation, visceral hypersensitivity, gastrointestinal motility and possibly stress-induced disorder in vivo. These effects counteract major pathophysiological causes of FD, and good clinical outcome is anticipated. Moreover, in FD there are some overlapping features with the other FGIDs and thus the effect of Motilitone may not be limited to FD.

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